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07/652,978

C07H'9/04

PATENT SPECIFICATION

(11) 1243213

1243213

NO DRAWINGS

- (21) Application No. 33243/69 (22) Filed 11 July 1968
 - (31) Convention Application No. 654 056 (32) Filed 18 July 1967
 - (31) Convention Application No. 709 234 (32) Filed 29 Feb. 1968 in
 - (33) United States of America (US)
 - (45) Complete Specification published 18 Aug. 1971
 - (51) International Classification C 07 f 9/38, 9/40, 9/44, 9/54
 - (52) Index at acceptance
- C2C P1L1 P2E12B P2E13 P2E14 P2E19B P2E19D P2E19E
P2E20 P2E23 P2E25B P2E26A P2E26B P2E26D
P2L12B P2L20 P2L26D P2L27 P2L29A P3B12A
P3B12B P3B13 P3B14A P3B16 P3B18C P3B19B
P3B19C P3B19D P3B19E P3B20 P3B21 P3C12B
P3C20 P3C21 P3C27 P3C29A P5A P5B P6 P7 P8



(54) IMPROVEMENTS IN OR RELATING TO PHOSPHORYLATED PHOSPHONIUM YLIDS

(71) We, SYNTAX CORPORATION, a Panamanian Corporation of Apartado Postal

ERRATA

SPECIFICATION No. 1,243,213

- Page 2, line 53, for "3-methylbutylidene-triphenylphosphorane;" read "3-methylbutylidenetriphenylphosphorane;"
- Page 4, line 1, for "pentameylth" read "penta-methyl"
- Page 4, line 7, for "thioester" read "trithio-ester"
- Page 6, line 17, for "crbonate," read "carbonate"
- Page 6, line 31, for "penol," read "phenol"
- Page 7, line 16, for "is" read "in"
- Page 8, line 27, after "substituents," insert "e.g. hydroxyl groups; hydroxyl derivatives, such as alkoxy,"
- Page 9, line 5, for "phosphonte" read "phosphonate"
- Page 10, line 4, for "6-azactosin-1-yl," read "6-azacytosin-1-yl,"
- Page 12, line 34, for "3',5'-" read "3',5'."
- Page 14, line 6, for "diemthyldiphenyl-" read "dimethyldiphenyl-"
- Page 17, line 11, for "β-O-ribo" read "β-D-ribo"
- Page 18, line 31, for "dethylaminoethyl" read "diethylaminoethyl"
- Page 19, line 21, for "[-(5,6-" read "[1-(5,6-"
- Page 20, line 28, after "obtained" insert "dimethyl"
- Page 22, line 25, for "arlkylxy" read "aralkyl-oxy"

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THE PATENT OFFICE
8th November 1971

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PATENT SPECIFICATION

(11) 1243213

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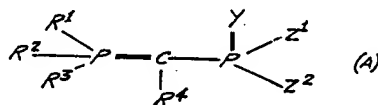
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 P2L12B P2L20 P2L26D P2L27 P2L29A P3B12A
 P3B12B P3B13 P3B14A P3B16 P3B18C P3B19B
 P3B19C P3B19D P3B19E P3B20 P3B21 P3C12B
 P3C20 P3C21 P3C27 P3C29A P5A P5B P6 P7 P8

(54) IMPROVEMENTS IN OR RELATING TO
PHOSPHORYLATED PHOSPHONIUM YLIDS

(71) We, SYNTEX CORPORATION, a Panamanian Corporation of Apartado Postal 7386, Panama, Panama, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new class of phosphorylated phosphonium ylids and to a process for the preparation of 5',6'-dideoxyhexofuranosylnucleoside 6'-phosphonic acids therewith. More particularly, the invention relates to a new class of phosphorylated phosphonium ylids having the following general formula:



wherein each of R^1 , R^2 and R^3 is lower alkyl or aryl or substituted aryl; or R^1 , R^2 and R^3 together are tri-*N*-piperidyl, tri-*N*-morpholinyl or tricyclohexyl; R^4 is hydrogen, lower alkyl, cyclohexyl, aryl, or substituted aryl; Y is oxygen or sulfur; each of Z^1 and Z^2 is the group OR^5 , SR^5 ,



or NR^5R^6 in which each of R^5 and R^6 is lower alkyl or lower alkenyl or aryl or substituted aryl, and each of R^7 and R^8 is lower alkyl, or aryl; or

Z^1 and Z^2 together are the group $\begin{array}{c} O \\ >R^9 \\ O \end{array}$, $\begin{array}{c} O \\ >R^9 \\ S \end{array}$ or $\begin{array}{c} S \\ >R^9 \\ S \end{array}$ in which R^9 is lower

alkylene or arylene.

The term "lower alkyl" means a straight or branched chain hydrocarbon group containing from 1 to 6 carbon atoms, inclusive, such as methyl, ethyl, *n*-propyl, *i*-butyl, *t*-butyl. The term "lower alkenyl" means a C_2-C_6 aliphatic hydrocarbyl group containing one carbon-carbon double bond such as allyl. The term "aryl" means a hydrocarbon group consisting of one or more aromatic rings and containing from 6 to 12 carbon atoms, inclusive, such as phenyl, benzyl, *o*-tolyl, *m*-tolyl, *p*-tolyl, 3,5-xyllyl, pentamethylphenyl, naphthyl. The term "substituted aryl" means an aryl group having one or more halo, nitro, alkoxy, or dialkylamino substituents in the aromatic ring such as *p*-chlorobenzyl, *p*-bromobenzyl, 2,4,6-trichlorophenyl, *p*-nitrophenyl, *p*-nitrobenzyl, *p*-anisyl, *p*-methoxybenzyl, *p*-dimethylaminophenyl. The term "lower

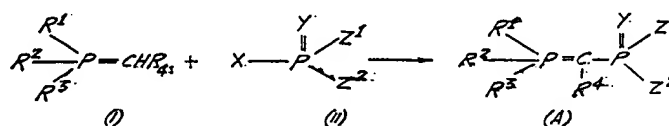
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SEE ERRATA SLIP ATTACHED

alkylene" means the group $-(CH_2)_n-$ in which n has a value of from 2 to 4, inclusive, such as ethylene, trimethylene and tetramethylene, said group can be further substituted with one or more alkyl or aryl groups such as in 2,2-dimethyltrimethylene, 1,2-diphenylethylene. The term "arylene" means an aryl group having two sites of attachment such as *o*-phenylene.

One aspect of the present invention provides a new class of phosphorylated phosphonium ylids which can be reacted with a wide variety of aldehydes and ketones, thereby providing unsaturated phosphonate or thiophosphonate derivatives thereof. Another aspect of the invention provides a process for reacting the novel phosphorylated phosphonium ylid with a nucleoside 5'-aldehyde to form the corresponding 5',6'-dideoxyhex-5'-enofuranosylnucleoside 6'-phosphonate. The latter unsaturated nucleoside is catalytically hydrogenated or chemically reduced and then converted to a corresponding 5',6'-dideoxyhexofuranosylnucleoside 6'-phosphonic acid by hydrolysis, hydrogenolysis, anionic dealkylation, or enzymatic action or combinations thereof.

The novel phosphorylated phosphonium ylids of Formula (A) can be prepared according to the following reaction:



wherein X is chloro or bromo; and all other substituents are as defined hereinabove.

In the preferred practice of the above sequence, a monosubstituted phosphonium ylid (I) is condensed under substantially anhydrous conditions with an appropriately disubstituted phosphoryl halide or thiophosphoryl halide (II) in a non-reactive organic solvent such as tetrahydrofuran, dioxane, dimethylformamide, dimethyl sulfoxide, benzene, diethyl ether, hexane, and mixtures thereof, at a temperature of from about 0°C to the reflux temperature of the solvent, for a period of about $\frac{1}{2}$ to about 12 hours. Preferably, the condensation is performed in diethyl ether, hexane, tetrahydrofuran, benzene, or mixtures thereof, with an appropriately disubstituted phosphoryl chloride or thiophosphoryl chloride (II), i.e. wherein X is chloro. Furthermore, reactions of the monosubstituted phosphonium ylid (I), wherein R^4 is hydrogen, alkyl or cyclohexyl, are preferably performed at room temperature for a period of about fifteen minutes to about one hour; and reactions of the monosubstituted phosphonium ylid (I), wherein R^4 is aryl or substituted aryl are preferably performed at the reflux temperature of the solvent for a period of about two hours or longer.

Although the molar proportion of the monosubstituted phosphonium ylid (I) to the disubstituted phosphoryl halide or thiophosphoryl halide (II) is not critical, a preferred embodiment of two moles of the monosubstituted phosphonium ylid per mole of the disubstituted phosphoryl halide or thiophosphoryl halide (II) is convenient.

In the practice of the above sequence, the reaction is advantageously performed in the presence of an atmosphere inert to the reaction such as a nitrogen atmosphere or an argon atmosphere. In addition, the monosubstituted phosphonium ylid (I) is generated *in situ* by conventional techniques known to those skilled in the art.

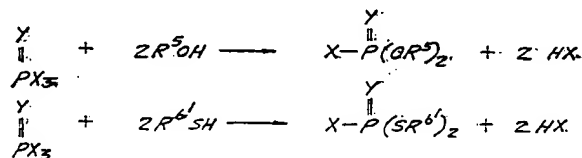
Included among the monosubstituted phosphonium ylids (I) which can be condensed with the disubstituted phosphoryl halide or thiophosphoryl halide (II) are methylenetrialkyl (including cycloalkyl)phosphoranes such as methylenetri-(*n*-butyl)phosphorane, methylenetriethylphosphorane, methylenetricyclohexylphosphorane, and the like; methylenealkylarylphosphoranes such as methyleneethyldiphenylphosphorane, methylenemethyldiphenylphosphorane, methylenediphenyl-*t*-butylphosphorane; methylenetriarylphosphoranes such as methylenetriphenylphosphorane, methylenetri-*p*-tolylphosphorane, methylenetri-*p*-anisylphosphorane; alkylidenetrialkylphosphoranes such as ethylidenetri-(*n*-butyl)phosphorane, alkylidenetrialkylphosphoranes such as ethylidenetriethylphosphorane; alkylidenetriarylphosphoranes such as ethylidenetriphenylphosphorane, propylidenetriphenylphosphorane, butylidenetriphenylphosphorane, pentylidenetriphenylphosphorane, cyclohexylmethylenetriphenylphosphorane, β -phenylethylidenetriphenylphosphorane, 3-methylbutylidenetriphenylphosphorane; arylmethylenetrialkylphosphoranes such as benzylidenetriethylphosphorane, benzylidenetricyclohexylphosphorane; arylmethylenetriarylphosphoranes such as benzylidenetriphenylphosphorane, *p*-nitrobenzylidenetriphenylphosphorane, *p*-methoxybenzylidenetriphenylphosphorane, benzylidenediphenyl-*p*-dimethylaminophenylphosphorane; and methylenetri-*N*-morpholinylphosphorane, methylenetri-*N*-piperidylphosphorane.

Additionally, other monosubstituted phosphonium ylids (I) which may be used

are prepared according to conventional procedures as described by S. Trippett, "Advances in Organic Chemistry", Interscience Publishing Co., New York (1960), Vol. 1, pages 83—102; S. Trippett, *Quarterly Review*, Vol. 16—17, pages 400—440 (1962—1963); A. W. Johnson, "Ylid Chemistry", Academic Press, New York (1966); and A. Maercker, "Organic Reactions", Vol. 14, John Wiley & Sons, Inc., New York (1965).

Included among the disubstituted phosphoryl halides or thiophosphoryl halides (IE) which can be used to prepare the novel phosphorylated phosphonium ylids (A) are disubstituted phosphorochloridates such as dimethyl phosphorochloridate, diethyl phosphorochloridate, di-allyl phosphorochloridate, di-*iso*-butyl phosphorochloridate, diphenyl phosphorochloridate, di-*o*-tolyl phosphorochloridate, di-*m*-tolyl phosphorochloridate, di-*p*-tolyl phosphorochloridate, *o*-phenylene phosphorochloridate, trimethylene phosphorochloridate, di-3,5-xylyl phosphorochloridate, di-(*p*-nitrophenyl) phosphorochloridate, 1,2-diphenylethylene phosphorochloridate, 2,2-dimethyltrimethylene phosphorochloridate, ethyl *p*-nitrophenyl phosphorochloridate, dibenzyl phosphorochloridate, di-(*p*-nitrobenzyl) phosphorochloridate, di-(pentamethylphenyl) phosphorochloridate, di-(*p*-bromobenzyl) phosphorochloridate; disubstituted phosphorobromidates such as dimethyl phosphorobromidate, diphenyl phosphorobromidate, methyl phenyl phosphorobromidate, *o*-phenylene phosphorobromidate; disubstituted phosphorochloridothioates such as O,O-diethyl phosphorochloridothioate, O,O-dimethyl phosphorochloridothioate, O,O-diphenyl phosphorochloridothioate, O,O-di-(*p*-chlorobenzyl) phosphorochloridothioate, O,S-diethyl phosphorochloridothioate, O-ethyl-O-*p*-nitrophenyl phosphorochloridothioate, O-methyl-O-2,4,5-trichlorophenyl phosphorochloridothioate; disubstituted phosphorochloridodithioates such as S,S-diethyl phosphorochloridodithioate, S,S-dibutyl phosphorochloridodithioate; disubstituted chloridotritioates such as diethyl phosphorochloridotritioate; disubstituted phosphorobromidothioates such as O,O-diethyl phosphorobromidothioate, O,O-diphenyl phosphorobromidothioate; disubstituted phosphorodiamidic chlorides such as tetraethylphosphorodiamidic chloride, phosphorodimorpholidic chloride, N,N'-dimethylphosphorodiamidic chloride, tetramethyl phosphorodiamidic chloride; disubstituted phosphorodiamidic bromides such as phosphorodimorpholidic bromide; mixed disubstituted phosphoramidochloridates such as O-phenyl N,N-diethylphosphoramidochloridate, O-ethyl N,N-diethylphosphoramidochloridate, O-*isopropyl* N,N-dimethylphosphoramidochloridate; mixed disubstituted phosphoramidochloridothioates such as S-butyl N,N-diethylphosphoramidochloridothioate, O-ethyl N,N-diethylphosphoramidochloridothioate, O-[2,4,5-trichlorophenyl]-N,N-dimethylphosphoramidochloridothioate.

Additionally, other disubstituted phosphoryl halides or thiophosphoryl halides (II) can be obtained by conventional techniques as described by G. N. Kosolapoff, "Organophosphorus compounds", John Wiley & Sons, Inc., New York (1950), Chapters 9 and 10. For example, the disubstituted phosphoryl halides or thiophosphoryl halides, i.e. wherein Z¹ and Z² together are the group (OR^s)₂ or (SR^s)₂ are prepared by adding two moles of a hydroxy or mercapto containing compound to one mole of phosphoryl chloride, phosphoryl bromide, thiophosphoryl chloride, or thiophosphoryl bromide in an essentially anhydrous non-reactive solvent such as chloroform, benzene, ether, tetrahydrofuran, dioxane, or mixtures thereof, at a temperature of from about room temperature to the reflux temperature of the solvent for a period of about 1 to 12 hours, as shown by the following equations and as described on pages 211—213 of the latter reference:

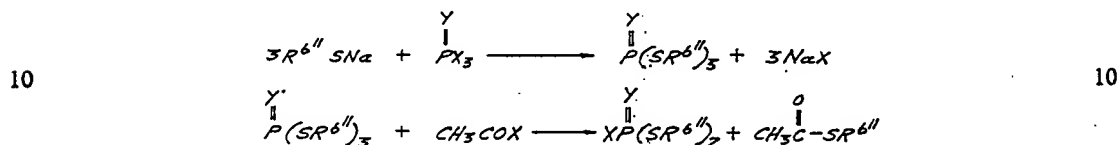


R^s being lower alkyl and all other substituents being as defined hereinabove. When the reaction is performed at the lower temperature, i.e. about room temperature, it is convenient to use two moles of a tertiary base such as 2,4,6-collidine, 2,6-lutidine or N,N-dimethylaniline to remove the liberated acid HX. Included among the hydroxy

containing compounds which can be reacted with the phosphorus halide PX₃ are alcohols such as methanol, ethanol, *n*-propanol, *iso*-butanol, *n*-amyl alcohol; phenols

such as phenol, *o*-cresol, *m*-cresol, *p*-cresol, 3,5-xylene, pentamethyl phenol, 4-chlorophenol; and mercaptans such as methanethiol, ethanethiol, *n*-propanethiol.

Other disubstituted phosphoryl halides and thiophosphoryl halides, i.e. wherein Z^1 and Z^2 together are $(SR^6)_2$ in which R^6 is aryl or substituted aryl are prepared by first adding three moles of the sodium salt of a thiophenol to one mole of phosphoryl chloride, phosphoryl bromide, thiophosphoryl chloride, or thiophosphoryl bromide, to obtain a thioester and second treating the trithioester with one mole of acetyl chloride or acetyl bromide as shown in the following equations and as described on page 218 of the latter reference.

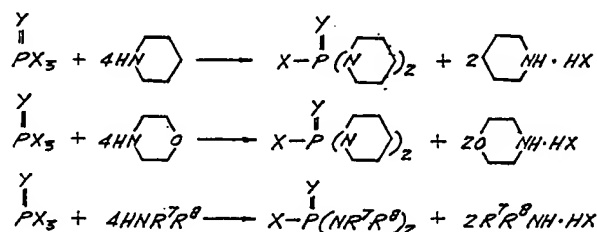


R^6'' being aryl or substituted aryl; and all other substituents are as defined hereinabove. Included among the thiophenols which can be reacted in the above manner, are thiophenol, thio-*o*-cresol, thio-*p*-cresol.

The disubstituted phosphorodiamidic halides, i.e. wherein each of Z^1 and Z^2 is the group



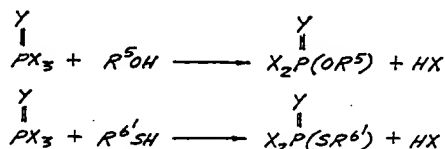
or NR^7R^8 , are prepared by adding four moles of a secondary amine to one mole of either phosphoryl chloride, phosphoryl bromide, thiophosphoryl chloride, or thiophosphoryl bromide, in an essentially anhydrous non-reactive organic solvent such as chloroform, benzene, ether, tetrahydrofuran, dioxane, or mixtures thereof, at a temperature of from about room temperature to the reflux temperature of the solvent, for a period of about 1 to 12 hours, as shown by the following equation and as described on pages 279 and 281—282 of the latter reference:

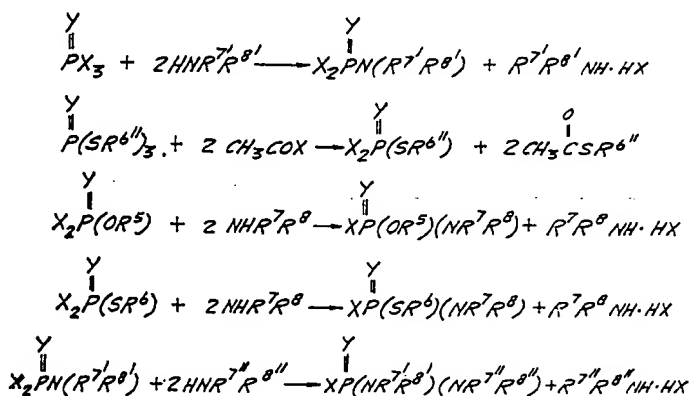


all substituents being as defined hereinabove. Included among the secondary amines

which can be reacted with the phosphorus halide PX_3 , are piperidine, morpholine; dialkyl amines such as dimethylamine, diethylamine, di-*n*-propylamine; diaryl amines such as diphenylamine; and mixed alkyl aryl amines such as *N*-methylaniline.

The mixed disubstituted phosphoryl halides or thiophosphoryl halides (II), i.e. wherein each of Z^1 and Z^2 are different, can be prepared by varying the molar proportions of reactants and proceeding in a two-step reaction sequence, as shown by the following equations;



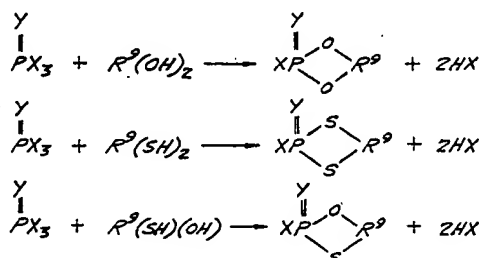


each of R^{r'} and R^{s'} being lower alkyl; and each of R^{r''} and R^{s''} being aryl; and all other substituents being as described hereinabove.

In addition, the disubstituted phosphoryl halides or thiophosphoryl halides, i.e.

5 wherein Z¹ and Z² together are the group $\begin{array}{c} \text{O} \\ \diagup \text{R}^{\text{g}} \\ \text{O} \end{array}$, $\begin{array}{c} \text{O} \\ \diagup \text{R}^{\text{g}} \\ \text{S} \end{array}$ or $\begin{array}{c} \text{S} \\ \diagup \text{R}^{\text{g}} \\ \text{S} \end{array}$ can be prepared 5

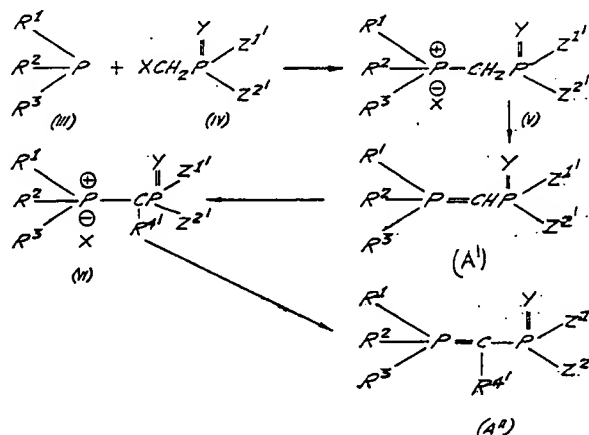
by adding one mole of a dihydroxy containing compound, a dimercapto containing compound or a monohydroxy monomercapto compound to one mole of phosphoryl chloride, phosphoryl bromide, thiophosphoryl chloride, or thiophosphoryl bromide under essentially the same anhydrous conditions as described above, and as shown by the following equations: 10



all substituents being as defined above. When the reaction is performed at the lower temperature, i.e. at about room temperature, it is convenient to use two moles of a tertiary amine such as 2,4,6-collidine, 2,6-lutidine, N,N-dimethylaniline, to remove the liberated acid HX. Included among the compounds of the formulas R^g(OH)₂, 15

R^g(SH)₂, and R^g(SH)(OH) which can be reacted with the phosphorus halide PX₃, are dihydroxy compounds such as ethylene glycol, trimethylene glycol, tetramethylene glycol, 2,2-dimethyltrimethylene glycol, 1,2-diphenylethylene glycol, catechol; dimercapto compounds such as 1,2-ethanedithiol, 1,3-propanedithiol, 1,4-butanedithiol, 20 1,2-benzenedithiol; and monohydroxy monomercapto compounds such as 2-mercaptoethanol, 3-mercaptopropanol, monothiocatechol.

As a first alternative, some of the novel phosphorylated phosphorus ylids of the present invention can be prepared according to the following reaction sequence:



wherein R¹ is lower alkyl or cyclohexyl; each of Z¹ and Z² is the group OR³,



or NR³ in which R³ is aryl or substituted aryl; and all other substituents being as defined hereinabove.

In the preferred practice of this alternative method, a trisubstituted phosphine (III) is allowed to react under substantially anhydrous conditions with an appropriately disubstituted halomethylphosphonic acid or halomethylphosphonothioic acid (IV) in a non-reactive organic solvent such as tetrahydrofuran, dioxane, benzene, dimethylformamide, or mixtures thereof, at room temperature to the reflux temperature of the solvent for a period of about 15 minutes to 24 hours, to afford a phosphorylated phosphonium halide salt (V). The latter salt (V) is converted to a corresponding phosphorylated phosphonium ylid (A') by treatment with an aqueous solution of a base, said solution optionally containing an organic solvent such as a lower monohydric alcohol such as methanol, ethanol; or a cyclic water-miscible ether such as dioxane, tetrahydrofuran. Bases particularly useful for this purpose are potassium hydroxide, sodium hydroxide, sodium ethoxide, sodium carbonate, pyridine. The conversion is effected at room temperature for a period of 5 minutes to 24 hours, a period of 15 minutes being preferred.

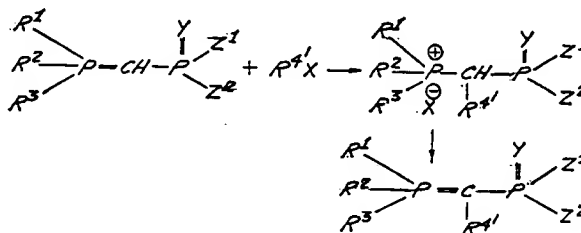
The thus-obtained novel ylid (A') is alkylated, if desired, by treatment with a halide of the formula R⁴X in a non-reactive organic solvent such as ethyl acetate, benzene, dioxane, dimethylformamide, at an elevated temperature, e.g. the reflux temperature of the solvent for a period of about 15 minutes to 3 hours to afford a corresponding alkylated phosphorylated phosphonium salt (VI). The latter salt (VI) is converted to a corresponding ylid (A'') by treatment with a base as described hereinabove for the unalkylated salt (V).

The trisubstituted phosphines (III) which can be used to prepare some of the novel phosphorylated phosphonium ylids (A' and A'') are described in the literature cited above.

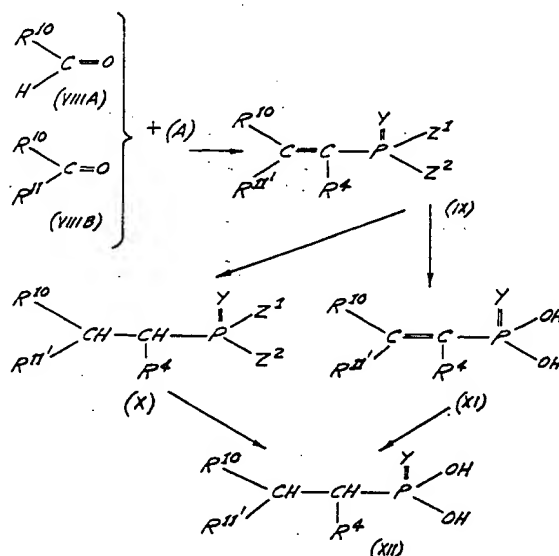
The disubstituted halomethylphosphonic acids or halomethylphosphonothioic acids (IV) can be prepared by adding a phenol, a secondary amine, or combinations thereof, in a stepwise manner, to chloromethylphosphonic acid dichloride, bromomethylphosphonic acid dichloride, chloromethylphosphonothioic dichloride, or bromomethylphosphonothioic dichloride, bromomethylphosphonic acid dibromide, bromomethylphosphonothioic acid dibromide, either alone or in the presence of a non-reactive organic solvent such as tetrahydrofuran, dioxane, benzene, or mixtures thereof, at reflux for a period of about four to twelve hours. The molar proportions of materials are varied, and the reaction is to be performed in a step-wise manner depending on the particular material (IV) being prepared, by procedures such as described hereinabove the preparation of the mixed disubstituted phosphoryl halides or thiophosphoryl halides (II).

$$\begin{array}{c}
 R^1 \\
 \diagdown \\
 R^2 - P = CHR_4 + \begin{array}{c} Z^1 \quad O \quad O \quad Z^1 \\ \diagdown \quad \diagup \quad \diagdown \quad \diagup \\ Z^2 - P - O - P - Z^2 \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ Z^2 \quad Z^2 \end{array} \\
 \diagup \\
 R^3
 \end{array}
 \quad (i) \quad
 \begin{array}{c}
 R^1 \\
 \diagdown \\
 R^2 - P - C - P - Z^1 \\
 \diagup \quad | \quad \diagup \quad \diagdown \\
 R^3 \quad R^4 \quad Z^2
 \end{array}
 \quad (A^{III})
 \quad + \quad
 \begin{array}{c}
 R^1 \\
 \diagdown \\
 R^2 - P^+ - CH_2 \\
 \diagup \quad | \\
 R^3 \quad R^4
 \end{array}
 \quad + \quad
 \begin{array}{c}
 O \quad O \\
 \diagdown \quad \diagup \\
 O - P - Z^2 \\
 \diagup \quad \diagdown \\
 Z^2
 \end{array}$$

As a third alternative, some of the novel phosphorylated phosphonium ylids of the present invention, i.e. those of Formula (A) in which R⁴ is lower alkyl or cyclohexyl, can be prepared, as described herein above in the first alternative method, according to the following reaction sequence:



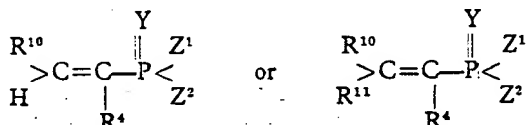
The phosphorylated phosphonium ylids (A) are valuable intermediates which can be reacted with a wide variety of aldehydes and ketones, thereby providing unsaturated phosphonate and thiophosphonate derivatives thereof. Thus, the present invention provides a valuable synthetic route for the preparation of phosphonic acids and thiophosphoric acids therefrom, as shown by the following reaction sequence:



wherein each of R^{10} >C=O and R^{10} >C=O is an aldehyde and ketone, respectively;
 H R^{11}
 R^{11} being hydrogen or R^{11} ; and all other substituents being as defined herein.

In the preferred practice of the latter reaction sequence, the phosphorylated phosphonium ylid (A) is allowed to react with a carbonyl compound of Formulas (VIII A) and (VIII B), respectively, either alone or in an organic solvent inert to the reaction such as tetrahydrofuran, dioxane, dimethylformamide, dimethyl sulfoxide, methanol, ethanol, acetonitrile, or mixtures thereof, at a temperature of 25°C to the reflux temperature of the solvent but preferably at about 25°C for a period of from 1 to 48 hours, to form a corresponding α,β -unsaturated phosphonate or thiophosphonate derivative (IX).

Any aldehyde, i.e. R^{10} >C=O or ketone, i.e. R^{10} >C=O , can be reacted with the
 H R^{11}
 phosphorylated phosphonium ylids of the present invention to form a corresponding α,β -unsaturated phosphonate or thiophosphonate derivative thereof, i.e.



For example, the carbonyl compounds of Formulas (VIII A) and (VIII B) may be any aldehyde or ketone of the aliphatic, alicyclic, aromatic, or heterocyclic series.

Included among the aliphatic, alicyclic and aromatic groups which R^{10} and R^{11} can represent are alkyl (including saturated and unsaturated, straight and branched chain alkyl and cycloalkyl) and aryl (including alkaryl and aralkyl) groups, such as methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, amyl, hexyl, heptyl, octyl, allyl, methallyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclohexyl, cycloheptyl, cyclohexenyl, phenyl, tolyl, xyl, benzyl, as well as fused ring structures, such as indanyl, indenyl, naphthyl, acenaphthyl, phenanthryl, and cyclopentanopolyhydrophenanthryl rings, all of which can either be unsubstituted or substituted with one or more non-interfering substituents, e.g. methoxy and acyloxy, e.g. acetoxy groups; nitro groups; amino groups; alkylamino groups, such as methylamino, dimethylamino and diethylamino groups; haloge, e.g. fluorine or chlorine; carbonyl derivatives; such as enol ether, acetal and ketal groups.

The thus-obtained α,β -unsaturated phosphonate (IX), i.e. wherein Y is oxygen, is catalytically hydrogenated at room temperature by conventional techniques such as in the presence of a palladium on an inert support catalysts such as palladium-on-barium sulfate, palladium-on-calcium carbonate, in a lower alcoholic solvent such as methanol, ethanol and the like, to form a corresponding saturated phosphonate (X).

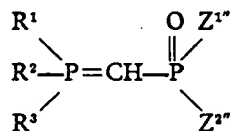
Alternatively, the α,β -unsaturated phosphonate (IX) is reduced by treatment with a diimide at room temperature in an inert non-reactive solvent such as methanol, ethanol, ethyl acetate, or mixtures thereof, for a period of about one to about twenty-four hours to afford the corresponding saturated phosphonate (X).

The thus-obtained α,β -unsaturated thiophosphonates (IX), i.e. wherein Y is sulfur, which adversely affects the efficiency of the palladium catalyst, as well as the α,β -unsaturated phosphonate (IX) having one or more groups such as nitro, allyl, which would be simultaneously reduced, are reduced by the diimide method as described above to afford the corresponding saturated thiophosphonate and phosphonates (X).

Each of the Z^1 and Z^2 groups in the thus-obtained α,β -saturated phosphonate or thiophosphonate (X) is removed by hydrolysis, hydrogenolysis, anionic dealkylation, enzymatic action, or combinations thereof, under a variety of different conditions to afford the α,β -saturated phosphonic acid or phosphonothioic acid (XII). The variety of conditions is dependent upon the nature of the Z^1 and Z^2 groups so that the removal of the first group and then a second group can be effected in a step-wise manner or the removal of both groups can be effected in a one-step procedure as will be discussed in more detail below.

Alternatively, the α,β -unsaturated phosphonate or thiophosphonate (IX) is converted to the corresponding α,β -unsaturated phosphonic acid (XI) by hydrolysis, hydrogenolysis, anionic dealkylation, enzymatic action, or combinations thereof, and the latter α,β -unsaturated phosphonic acid or thiophosphonic acid (XI) is converted to saturated phosphonic acid or thiophosphonic acid (XII) as described hereinabove.

Furthermore, the phosphorylated phosphonim ylids having the general formula:



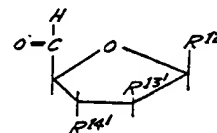
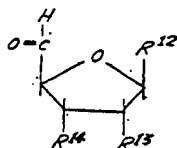
wherein each of $Z^{1''}$ and $Z^{2''}$ is the group OR^5 , SR^6 ,



or $NR'R''$ in which each of R^5 and R^6 is lower alkyl, lower alkenyl, aryl or substituted aryl, and each of R'' and R''' is lower alkyl;

or $Z^{1''}$ and $Z^{2''}$ together are the group $\begin{array}{c} O \\ >R^9 \\ O \end{array}$ in which R^9 is arylene; and

all other substituents being as defined hereinabove, are valuable intermediates in the preparation of nucleoside 6'-phosphonic acids. For example, when R^{10} in the general formula $\begin{array}{c} R^{10} \\ >C=O \\ H \end{array}$ given above for an aldehyde, represents a particular class of substituted tetrahydrofurfuryl groups, i.e. those having the structures:



wherein R^{12} is a substituted or unsubstituted pyrimidine or purine base, e.g. uracil-1-yl, cytosin-1-yl, 4-chloro-1,2-dihydropyrimidin-2-on-1-yl, 5-bromouracil-1-yl, 5-bromocytosin-1-yl, 5-chlorouracil-1-yl, 5-chlorocytosin-1-yl, 5-iodouracil-1-yl,

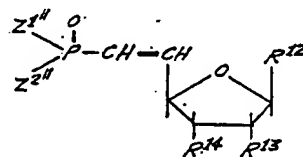
5-iodocytosin-1-yl, 5-fluorouracil-1-yl, 5-fluorocytosin-1-yl, thymine-1-yl, 5-methylcytosin-1-yl, 5-trifluoromethyluracil-1-yl, 5-trifluoromethylcytosin-1-yl, 5-aminouracil-1-yl, 5-aminocytosin-1-yl, 5-methylaminouracil-1-yl, 5-methylaminocytosin-1-yl, 5-hydroxyuracil-1-yl, 6-azauracil-1-yl, 6-azactosin-1-yl, 4-chloro-6-aza-1,2-dihydropyrimidin-2-on-1-yl, 6-azathymine-1-yl, hypoxanthine-9-yl, adenine-9-yl, 6-dimethylaminopurine-9-yl, 2-chloroadenine-9-yl, 6-chloropurine-9-yl, 6-mercaptopurine-9-yl, guanine-9-yl, xanthine-9-yl, 2,6-dichloropurine-9-yl, 2,6-bis(methylamino)purine-9-yl, 8-azaadenine-9-yl, 8-azaguanine-9-yl, 7-deazaadenine-9-yl;

each of R^{13} and $R^{13'}$ is hydrogen, hydroxy, alkoxy or acyloxy;

each of R^{14} and $R^{14'}$ is hydrogen, hydroxy, alkoxy or acyloxy; or

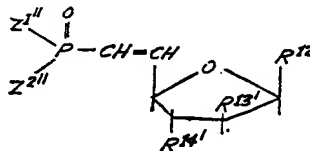
R^{13} and R^{14} together are acetal or ketal group, e.g. isopropylidenedioxy, *p*-anisylidenedioxy, the starting material is a nucleoside 5'-aldehyde and will be converted by reaction with the latter ylid using the process of the present invention to the corresponding intermediary 5',6'-dideoxyhex-5'-enofuranosyl nucleoside 6'-phosphonate

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and arabinohex-5'-enofuranosyl nucleoside 6'-phosphonate, respectively

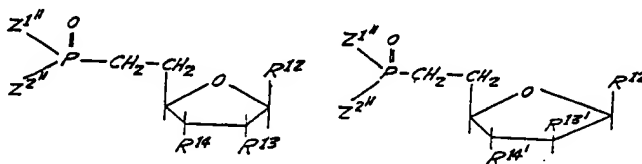


wherein all substituents are as defined hereinabove.

The intermediary α,β -unsaturated phosphonates are converted by catalytic hydrogenation or diimide reduction as described hereinabove to afford a corresponding saturated phosphonate, i.e., nucleoside 6'-phosphonates having the formulas:

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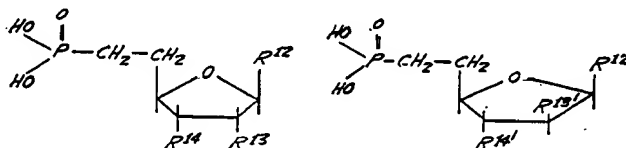


wherein all substituents are as defined hereinabove.

As exemplified by the following procedures, both of the $Z^{1''}$ and $Z^{2''}$ groups in the latter compound can be removed by hydrolysis, hydrogenolysis, anionic dealkylation, enzymatic action or combinations thereof, to afford a corresponding nucleoside 6'-phosphonic acid, i.e.

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wherein all substituents are as defined hereinabove. For example, where each of $Z^{1''}$ and $Z^{2''}$ represents the group OR^5 in which R^5 is lower alkyl, the alkyl groups are removed by heating with an iodide salt such as sodium iodide, in an aprotic dipolar solvent, such as dimethylformamide, at a temperature of about 140°C to 150°C for about 16 to 48 hours. Where each of $Z^{1''}$ and $Z^{2''}$ represents the group OR^5 in which R^5 is aryl or substituted aryl, the aryl or substituted aryl groups are removed by alkaline hydrolysis in a step-wise manner by reacting first at room temperature in an

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aqueous organic solution of a strong alkali metal hydroxide such as lithium hydroxide or sodium hydroxide in aqueous dioxane, tetrahydrofuran, acetonitrile, for about 30 minutes to two hours. The second OR³ group is removed by refluxing with saturated aqueous barium hydroxide solution for 30 minutes to two hours. Alternatively, the second OR³ group is removed by enzymatic action by incubation in the presence of a snake venom phosphodiesterase such as that present in the venom of *Crotaleus adamanteus*. Where each of Z^{1''} and Z^{2''} represents the group OR³ in which R³ is a lower alkenyl or aralkyl group, more specifically an allyl group, a benzyl group or a substituted benzyl group, the allyl, benzyl or substituted benzyl groups are removed by hydrogenolysis at room temperature over a palladium on an inert support catalyst such as a palladium-on-barium sulfate catalyst under the slight positive pressure of hydrogen for a period of about two to six hours. Where each of Z^{1''} and Z^{2''} represents the group OR³ in which R³ is phenyl, substituted phenyl or naphthyl, the nucleoside 6'-phosphonic acid can be prepared by subjecting the nucleoside 6'-phosphonate to transesterification by treatment with a primary alcohol in dipolar organic solvent in the presence of a base followed by anionic dealkylation in the case of dialkyl phosphonates or hydrogenolysis in the case of diaralkyl phosphonates. Suitable primary alcohols include the saturated aliphatic alcohols such as methanol, ethanol, 2,2,2-trichloroethanol, and the like of up to six carbon atoms and aralkyl alcohols such as benzyl alcohol, methylbenzyl alcohol, β -phenylethanol, 3-phenyl-1-propanol, 4-phenyl-1-butanol. Suitable bases for generating the alkoxide or aralkoxide include the alkali metal hydrides, alkali metals, alkali metal t-butoxides, triethylamine. The reaction is carried out under anhydrous conditions in a dipolar organic solvent such as dimethylformamide, dimethylsulfoxide. Where each of Z^{1''} and Z^{2''} represents the group SR⁶ in which each of R⁶ is lower alkyl, aryl or substituted aryl, the alkylthio, arylthio or substituted arylthio groups are removed in a step-wise manner by treatment with a mild alkali such as alkali metal bicarbonate or an alkali metal carbonate in an aqueous organic solvent such as aqueous methanol, acetone, at room temperature for a period of about 30 minutes to six hours to remove the first group and then by treatment with an aqueous acetone solution containing a molar equivalent of iodine to remove the second group, as described by A. L. Nussbaum et al., *J. Am. Chem. Soc.* 87, 2513-4 (1965). Where

$$\begin{array}{c} \text{O} \\ | \\ \text{Z}^{1''} \text{ and } \text{Z}^{2''} \text{ together represent the group } >\text{R}^9 \text{ in which R}^9 \text{ is arylene such as} \\ \text{O} \end{array}$$

o-phenylene, the o-arylene group is removed in a step-wise manner by treatment with water to form an intermediary o-hydroxyphenyl monoester and second by treatment with an aqueous solution of bromine, essentially hypobromous acid, to cleave the o-hydroxyphenyl group, as described by T. A. Khawaja and C. B. Reese, *J. Am. Chem. Soc.*, 88, 3446-7 (1966). Where each of Z^{1''} and Z^{2''} represents the group



the morpholinyl groups are removed by aqueous hydrolysis with an acidic ion-exchange resin such as sulphonated polystyrene beads cross-linked with 8% divinylbenzene or with an aqueous inorganic acid such as hydrochloric acid. Where each of Z^{1''} and Z^{2''} represents the group



or NR⁷R⁸, the piperidyl groups or the dialkylamino groups are removed by aqueous hydrolysis with an acidic ion-exchange resin in the acid form or with an aqueous inorganic acid such as aqueous hydrochloric acid.

Alternatively, removal of the Z^{1''} and Z^{2''} groups can be effected by one of the procedures described hereinabove prior to the catalytic hydrogenation or diimide reduction procedure, as described hereinabove, to obtain the nucleoside 6'-phosphonic acids.

The novel phosphorylated phosphonium ylids of the present invention are versatile reagents useful in converting carbonyl compounds into phosphonates, free phosphonic acids or phosphonic acid salts. They are useful as intermediates in the preparation of, for example, insecticides, herbicides, oil additives, detergents, lubricant and oil additives,

flame retardants, anti-oxidants and nucleoside phosphonates, phosphonic acids and phosphonic acid salts. Insecticides such as the alkyl *p*-nitrophenyl alkylphosphonates and thio analogs thereof can be prepared by condensing acetaldehyde, propanal, butanal, with the appropriately substituted phosphorylated phosphonium ylid, namely
5 wherein Y is oxygen or sulfur; Z¹ is O-ethyl and Z² is O-*p*-nitrophenyl, followed by reducing the intermediary α,β -unsaturated phosphonate or thiophosphonate by the diimide reduction. Herbicides such as the diesters of octylphosphonic acid can be prepared by condensing heptanal with the appropriately substituted phosphorylated phosphonium ylid, namely wherein Y is oxygen and each of Z¹ and Z² is the group
10 OR^s in which R^s is lower alkyl, aryl or substituted aryl followed by catalytic hydrogenation or diimide reduction of the intermediary α,β -unsaturated phosphonate. Oil additives such as the dialkyl styryl-phosphonates can be prepared by condensing benzaldehyde with the appropriately substituted phosphorylated phosphonium ylid, namely wherein Y is oxygen and each of Z¹ and Z² is the group OR^s in which R^s is
15 lower alkyl. The nucleoside 6'-phosphonic acids prepared according to the process of this invention and derivatives prepared therefrom are isosteric with the natural nucleoside 5'-phosphates and derivatives thereof and can be used in the same manner as and as a replacement for the latter compounds. The nucleoside 6'-phosphonic acids and derivatives thereof differ from the known nucleoside 5'-phosphates and derivatives thereof in that the former contains a P—CH₂—C group in place of the natural
20 P—O—C group, thereby conferring greater metabolic stability to the former. The nucleoside 6'-phosphonic acids and derivatives thereof are not sensitive to cell wall phosphatase and hence are not cleaved into the parent materials during entrance into the cell. The nucleoside 6'-phosphonic acids and derivatives thereof are also useful intermediates for the preparation of cyclic 3',6'-phosphonates. This conversion can be accomplished by treating the nucleoside 6'-phosphonic acid with a dehydrating agent, e.g. a carbodiimide such as N,N'-dicyclohexylcarbodiimide, N,N'-di-*p*-tolyl-
25 carbodiimide, in a basic solvent such as pyridine according to the procedure of Smith et al., *J. Am. Chem. Soc.*, 83, 698, (1961); U.S. Patent 3,300,479; French 2883M (1964); or French 3249M (1965). The cyclic 3',6'-phosphonates can be used in the same manner as and as a replacement for nucleoside cyclic 3',5'-phosphates such as adenosine 3',5'-cyclic phosphate which are useful, for example, for the control of steroid production, the treatment of hypotension and as vasodilators. The cyclic 3',6'-phosphonates being much less susceptible to hydrolysis than are the cyclic 3',5'-
30 phosphates have the advantage of a longer biological half life.

The following examples are set forth to illustrate the present invention.

EXAMPLE 1

To a mixture of 7.14 g. (20 mmoles) of methyltriphenylphosphonium bromide in 100 ml. of ether, cooled to 20°C and under a nitrogen atmosphere, is added
40 12.6 ml. of a 1.6M solution of *n*-butyl lithium in hexane (20 mmoles). The mixture is allowed to stand at 20°C for an additional one-half hour, at which time a yellow solution of methylenetriphenylphosphorane is present. To this mixture is then added dropwise a solution of 2.68 g. (10 mmoles) of diphenyl phosphorochloridate in 50 ml. of ether over a period of five minutes, and the resulting reaction mixture is allowed
45 to stand for a period of 15 minutes. The reaction mixture is then extracted with two 100 ml. portions of 3N hydrochloric acid. The combined acid extracts are washed with ether, and then carefully neutralized by the dropwise addition of 4N aqueous sodium hydroxide to afford a precipitate. The precipitate is collected by filtration, washed with water and then hexane to yield diphenyl triphenylphosphoranylidene methylphosphonate which is further purified by recrystallization from ethyl acetate:hexane.
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In a similar manner by repeating the above procedure with one exception, namely substituting first methyldiphenyl-*t*-butylphosphonium bromide, second tetramethylphosphonium bromide, third methyltricyclohexylphosphonium bromide, and fourth dimethyldiphenylphosphonium bromide for methyltriphenylphosphonium bromide,
55 there are generated *in situ* the corresponding intermediary monosubstituted phosphonium ylids first methylenediphenyl-*t*-butylphosphorane, second methylenetrimethylphosphorane, third methylenetricyclohexylphosphorane, and fourth methylenemethyldiphenylphosphorane for methylenetriphenylphosphorane in the above procedure, and there are obtained, the corresponding diphenyl phosphoranylidene methylphosphonates,

namely first diphenyl diphenyl-*t*-butylphosphoranylidene-methylphosphonate, second diphenyl trimethylphosphoranylidene-methylphosphonate, third diphenyl tricyclohexylphosphoranylidene-methylphosphonate, and fourth diphenyl methyl-diphenylphosphoranylidene-methylphosphonate.

EXAMPLE 2

To a mixture of 1.78 g. of methyltriphenylphosphonium bromide in 25 ml. of ether, cooled to 20°C and under a nitrogen atmosphere, is added 3.10 ml. of 1.6M solution of *n*-butyl lithium in hexane. The mixture is allowed to stand at 20°C for an additional one-half hour, at which time a yellow solution of methylenetriphenylphosphorane is present. To this mixture is then added dropwise a solution of 0.74 g. of di-*o*-tolyl phosphorochloridate in 10 ml. of ether, and the resulting reaction mixture is allowed to stand at room temperature for a period of 15 minutes. The reaction mixture is then partitioned between 50 ml. of water and 50 ml. of benzene. The aqueous layer is separated and extracted with several portions of benzene. Then the combined organic phase and extracts are washed with water and dried over magnesium sulfate. After removing the magnesium sulfate by filtration, the organic phase is evaporated to dryness under reduced pressure to afford a colorless oil. The oil is recrystallized from ethyl acetate:hexane to afford di-*o*-tolyl triphenylphosphoranylidene-methylphosphonate as a white crystalline solid.

In a similar manner by repeating the above procedure with one exception, namely substituting first di-*m*-tolyl phosphorochloridate, second di-*p*-tolyl phosphorochloridate, and third di-3,5-xylol phosphorochloridate for the di-*o*-tolyl phosphorochloridate in the above procedure, there are obtained the corresponding diaryl triphenylphosphoranylidene-methylphosphonates, namely di-*m*-tolyl triphenylphosphoranylidene-methylphosphonate, di-*p*-tolyl triphenylphosphoranylidene-methylphosphonate and di-3,5-xylol triphenylphosphoranylidene-methylphosphonate, respectively.

EXAMPLE 3

To 100 ml. of anhydrous liquid ammonia, previously cooled in a Dry Ice-acetone bath and under an inert atmosphere of argon, are added 0.5 g. of metallic sodium and a few grains of ferric nitrate, and the resulting mixture is allowed to stir until it turns grey. Then 3.57 g. (10 mmoles) of methyltriphenylphosphonium bromide is added to the mixture. After stirring the mixture for 15 minutes, the ammonia is removed by evaporation leaving behind a residue. To this residue is then added 100 ml. of anhydrous tetrahydrofuran, and the resulting mixture is held at reflux for 20 minutes to expel any residual ammonia, then cooled and filtered through a sintered glass filter of medium porosity. To the filtrate is then added 1.34 g. (5 mmoles) of diphenyl phosphorochloridate and this mixture is then held at room temperature for a period of 30 minutes. The reaction mixture is then filtered and the filtrate evaporated to dryness to yield diphenyl triphenylphosphoranylidene-methylphosphonate which is further purified by recrystallization from ethyl acetate:hexane.

In a similar manner by repeating the above procedure with the phosphonium salts and phosphorylating agents indicated in the table, there are obtained the following products:

| Phosponium Salts | Phosphorylating Agents | Products |
|------------------------------------|---|--|
| ethyltriphenylphosponium bromide | diphenylphosphorochloridate | diphenyl [1-triphenylphosphoranylidene]ethylphosphonate |
| methyltriphenylphosponium bromide | diethyl phosphorochloridate | diethyl triphenylphosphoranylidene-methylphosphonate |
| dimethyldiphenylphosponium bromide | diethyl phosphorochloridate | diethyl methyl-diphenylphosphoranylidene-methylphosphonate |
| methyltriphenylphosponium bromide | tetra-(<i>p</i> -nitrophenyl) pyrophosphate | di-(<i>p</i> -nitrophenyl) triphenylphosphoranylidene-methylphosphonate |
| methyltriphenylphosponium bromide | dibenzyl phosphorochloridate | dibenzyl triphenylphosphoranylidene-methylphosphonate |
| methyltriphenylphosponium bromide | di-(<i>p</i> -bromobenzyl) phosphorochloridate | di-(<i>p</i> -bromobenzyl) triphenylphosphoranylidene-methylphosphonate |
| methyltriphenylphosponium bromide | diphenyl phosphorochloridothioate | diphenyl triphenylphosphoranylidene-methylthiophosphonate |
| methyltriphenylphosponium bromide | di-(<i>p</i> -nitrobenzyl) phosphorochloridate | di-(<i>p</i> -nitrobenzyl) triphenylphosphoranylidene-methylphosphonate |
| methyltriphenylphosponium bromide | <i>o</i> -phenylene phosphorobromidate | <i>o</i> -phenylene triphenylphosphoranylidene-methylphosphonate |
| methyltriphenylphosponium bromide | 2,2-dimethyltrimethylene phosphorochloridate | 2,2-dimethyltrimethylene triphenylphosphoranylidene-methylphosphonate |

EXAMPLE 4

To 100 ml. of anhydrous liquid ammonia, previously cooled in a Dry Ice-acetone bath and under an inert atmosphere of argon, are added 0.5 g. of metallic sodium and a few grains of ferric nitrate, and the resulting mixture is allowed to stir until it turns grey. Then 3.57 g. (10 mmoles) of methyltriphenylphosphonium bromide is added to the mixture. After stirring the mixture for 15 minutes, the ammonia is removed by evaporation leaving behind a residue. To this residue is then added 100 ml. of anhydrous tetrahydrofuran, and the resulting mixture is held at reflux for 20 minutes to expel any residual ammonia, then cooled and filtered through a sintered glass filter of medium porosity. To the filtrate is then added 1.27 g. (5 mmoles) of phosphorodimorpholidic chloride and this mixture is then held at 40°C for a period of one hour. The reaction mixture is then filtered and the filtrate evaporated to dryness to yield triphenylphosphoranylidene-methylphosphonodimorpholidate which is further purified by recrystallization from ethyl acetate:hexane.

In a similar manner by repeating the above procedure with the phosphonium salts and phosphorylating agents indicated in the table, there are obtained the following products:

| Phosphonium Salts | Phosphorylating Agents | Products |
|---|---|---|
| methyltriphenylphosphonium bromide | phosphorodimorpholidic bromide | triphenylphosphoranylidene-methylphosphonodimorpholidate |
| methyltriphenylphosphonium bromide | diethyl phosphorochloridothioate | diethyl triphenylphosphoranylidene-methylthiophosphonate |
| methyltriphenylphosphonium bromide | N,N'-dimethylphosphorodianilidic chloride | triphenylphosphoranylidene-methylphosphonodi(N-methylanilidate) |
| tetramethylphosphonium bromide | O,O-diphenyl phosphorochloridothioate | diphenyl trimethyl phosphoranylidene-methylthiophosphonate |
| methyltri- <i>n</i> -butylphosphonium bromide | phosphorodimorpholidic bromide | tri- <i>n</i> -butylphosphoranylidene-methylphosphonodimorpholidate |

EXAMPLE 5

To 100 ml. of anhydrous liquid ammonia, previously cooled in a Dry Ice-acetone bath and under an inert atmosphere of argon, are added 0.5 g. of metallic sodium and a few grains of ferric nitrate, and the resulting mixture is allowed to stir until it turns grey. Then 4.34 g. (10 mmoles) of benzyltriphenylphosphonium bromide is added to the mixture. After stirring the mixture for 15 minutes, the ammonia is removed by evaporation leaving behind a residue. To this residue is then added 100 ml. of anhydrous tetrahydrofuran, and the resulting mixture is held at reflux for 20 minutes to expel any residual ammonia, then cooled and filtered through a sintered glass filter of medium porosity. To the filtrate is then added 1.34 g. (5 mmoles) of diphenyl phosphorochloridate and this mixture is then held at 65°C for a period of two hours. The reaction mixture is then filtered and the filtrate evaporated to dryness to yield diphenyl triphenylphosphoranylidenebenzylphosphonate which is further purified by recrystallization from ethyl acetate:hexane.

In a similar manner by repeating the above procedure with the phosphonium salts and phosphorylating agents indicated in the Table, there are obtained the following products:

| Phosphonium Salts | Phosphorylating Agents | Products |
|---|---|---|
| benzyltriphenylphosphonium bromide | diethyl phosphorochloridate | diethyl triphenylphosphoranylidenebenzylphosphonate |
| benzyl dimethyl phenylphosphonium bromide | diphenyl phosphorochloridate | diphenyl dimethylphenylphosphoranylidenebenzylphosphonate |
| <i>p</i> -nitrobenzyltriphenylphosphonium bromide | diphenyl phosphorochloridothioate | diphenyl triphenylphosphoranylidene- <i>p</i> -nitrobenzylthiophosphonate |
| benzyltricyclohexylphosphonium bromide | di- <i>p</i> -tolyl phosphorochloridate | di- <i>p</i> -tolyl tri-cyclohexylphosphoranylidenebenzylphosphonate |

EXAMPLE 6

5 A mixture of 0.36 g. (1 mmole) of 2',3'-O-anisylideneuridine-5'-aldehyde [prepared in accordance with U.S. patent 3,248,380] and 0.508 g. (1 mmole) of diphenyl triphenylphosphoranylidene methylphosphonate in 10 ml. of tetrahydrofuran is allowed to stand at 37°C for a period of 16 hours. The reaction mixture is then chromatographed on a 1 meter×20 cm. glass plate coated with a 1.3 mm. layer of silicic acid. After development of the plate in the solvent mixture, isopropanol:chloroform (1:9), the main ultraviolet absorbing band ($R_F=0.5$) is eluted with acetone. After removing the solvent by evaporation under reduced pressure, there is obtained diphenyl [1-(2,3-O-anisylidene-5,6-dideoxy- β -D-ribo-hex-5-enofuranosyl)uracil] 6'-phosphonate as a white, homogeneous foam.

EXAMPLE 7

15 To a solution of 2.84 g. (10 mmoles) of 2',3'-O-isopropylideneuridine in 25 ml. of anhydrous dimethyl sulfoxide are added 6.2 g. (30 mmoles) of dicyclohexylcarbodiimide, 0.8 ml. (10 mmoles) of pyridine and 0.4 ml. (5 mmoles) of trifluoroacetic acid. The resulting solution is allowed to stand at 25°C for six hours, during which time dicyclohexylurea precipitates from the solution. At the end of the reaction, dicyclohexylurea is removed by filtration and washed with several portions of fresh, anhydrous dimethyl sulfoxide. To the combined filtrate and washings, is added 5.08 g. (10 mmoles) of diphenyl triphenylphosphoranylidene methylphosphonate, and the resulting mixture is allowed to stand at 37°C for 16 hours. At this point, 200 ml. of ethyl acetate is added, and the organic phase is washed with three 100 ml. portions of water, dried, filtered, and evaporated under reduced pressure to afford a pale yellow oil. A solution of the thus-obtained oil in chloroform is chromatographed on eight 1 meter×20 cm. glass plates coated with a 1.3 mm. layer of silicic acid. After development of the plates with ethyl acetate, two ultraviolet absorbing products are eluted from the plates with ethyl acetate. After removing the solvent from the faster moving product, there is obtained diphenyl [1-(5,6-dideoxy-2,3-O-isopropylidene- β -D-ribo-hex-5-enofuranosyl)uracil] 6'-phosphonate which is purified by recrystallization from aqueous ethanol. After removing the solvent from the slower moving product, there is obtained triphenylphosphine oxide.

35 In a similar manner by repeating the above procedure with two exceptions, namely substituting a molar amount of each of 2',3'-O-isopropylideneadenosine and diethyl triphenylphosphoranylidene methylphosphonate for 2',3'-O-isopropylideneuridine and diphenyl triphenylphosphoranylidene methylphosphonate, respectively, there is obtained the corresponding product, namely diethyl [9-(5,6-dideoxy-2,3-O-isopropylidene- β -D-ribo-hex-5-enofuranosyl)adenine] 6'-phosphonate.

EXAMPLE 8

40 A solution of 512 mg. (1 mmole) of diphenyl [1-(5,6-dideoxy-2,3-O-isopropylidene- β -D-ribo-hex-5-enofuranosyl)uracil] 6'-phosphonate in 30 ml. of methanol is

hydrogenated at 20°C in the presence of 0.2 g. of a pre-reduced 5% palladium-on-barium sulfate catalyst and under a slight positive pressure of hydrogen for two hours, at which time, the uptake of hydrogen reached the theoretical value. The catalyst is removed by filtration through diatomaceous earth and washed with methanol. The combined filtrate and washings are evaporated to dryness under reduced pressure to yield diphenyl [1-(5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hexofuranosyl)uracil] 6'-phosphonate as a white foam.

In a similar manner by repeating the above procedure with one exception, namely substituting a molar amount of diethyl [9-(5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hex-5-enofuranosyl)adenine] 6'-phosphonate for diphenyl [1-(5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hex-5-enofuranosyl)uracil] 6'-phosphonate, there is obtained the corresponding product, namely diethyl [9-(5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hexofuranosyl)adenine] 6'-phosphonate.

EXAMPLE 9

A solution of 0.50 g. of diphenyl [1-(5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hexofuranosyl)uracil] 6'-phosphonate in 20 ml. of 80% acetic acid is heated at 100°C for two hours. The solvent is then removed by evaporation under reduced pressure to yield a residue of diphenyl [1-(5,6-dideoxy-β-D-ribo-hexofuranosyl)uracil] 6'-phosphonate which is purified by repeated dissolution and evaporation from several quantities of ethanol.

In a similar manner by repeating the above procedure with one exception, namely substituting diethyl [9-(5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hexofuranosyl)adenine] 6'-phosphonate for diphenyl [1-(5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hexofuranosyl)uracil] 6'-phosphonate, there is obtained the corresponding product, namely diethyl [9-(5,6-dideoxy-β-D-ribo-hexofuranosyl)adenine] 6'-phosphonate.

EXAMPLE 10

To a solution of 119 mg. (0.25 mmole) of diphenyl [1-(5,6-dideoxy-β-D-ribo-hexofuranosyl)uracil] 6'-phosphonate in 10 ml. of dioxane and 10 ml. of water is added 1 ml. of 1N aqueous solution of lithium hydroxide. The resulting solution is allowed to stand at 20°C for one hour at which time the pH of the solution is adjusted to 7 by the addition of an acid-ion exchange resin. After removing the resin by filtration, the filtrate is reduced to dryness under reduced pressure to afford a residue. A solution of the thus-obtained residue in 10 ml. of water is chromatographed on a 1 meter×20 cm. glass plate coated with a 1.3 mm. layer of microcrystalline cellulose. After developing the plates in the solvent mixture, isopropanol: ammonium hydroxide: water (7:1:2), the ultraviolet absorbing material, having an R_F value of 0.5 to 0.6, is eluted with water. After removal of the water by evaporation under reduced pressure, there is obtained phenyl [1-(5,6-dideoxy-β-D-ribo-hexofuranosyl)uracil] 6'-phosphonic acid as a chromatographically homogeneous foam.

EXAMPLE 11

One milliliter of a solution containing 40 mg. (0.1 mmole) of phenyl [1-(5,6-dideoxy-β-D-ribo-hexofuranosyl)uracil] 6'-phosphonic acid, 60 μl. of 0.01M aqueous magnesium chloride, 40 μl. of a solution containing 10 mg./ml. of crude *Crotaleus adamanteus* venom in 0.5M tris(hydroxymethyl)aminomethane buffer at pH 8, 40 μl. of a 1M tris(hydroxymethyl)aminomethane buffer at pH 8, is incubated at 37°C for 24 hours. After this reaction time, the incubation mixture is then diluted with 25 ml. of water and chromatographed on a 1.5×20 cm. column containing 25 g. of diethyl-aminoethyl cellulose in the bicarbonate form. The column is washed with 200 ml. of water and then eluted with a linear gradient (0.002—0.2M) of aqueous triethyl-ammonium bicarbonate at pH 7.5. The main ultraviolet absorbing peak is collected and evaporated to dryness under reduced pressure to yield the bistriethylammonium salt of [1-(5,6-dideoxy-β-D-ribo-hexofuranosyl)uracil] 6'-phosphonic acid.

EXAMPLE 12

By repeating the procedure of Example 7 with two exceptions, namely substituting 3'-O-acetylthymidine and dibenzyl triphenylphosphoranylidene-methylphosphonate for 2',3'-O-isopropylideneuridine and diphenyl triphenylphosphoranylidene-methylphosphonate, respectively, there is obtained dibenzyl [1-(3-O-acetyl-2,5,6-trideoxy-β-D-erythro-hex-5-enofuranosyl)thymine] 6'-phosphonate.

EXAMPLE 13

A solution of 0.54 g. of dibenzyl [1-(3-O-acetyl-2,5,6-trideoxy- β -D-erythro-hex-5-enofuranosyl)thymine] 6'-phosphonate in 25 ml. of methanol is reduced at 25°C in the presence of 200 mg. of a pre-reduced 5% palladium-on-barium sulfate catalyst and under a slight positive pressure of hydrogen for a period of three hours. The catalyst is removed by filtration through diatomaceous earth, and washed with methanol. The combined filtrate and washings are evaporated to dryness under reduced pressure to yield [1-(3-O-acetyl-2,5,6-trideoxy- β -D-erythro-hexofuranosyl)thymine] 6'-phosphonic acid.

A solution of the 0.5 g. of the latter material in 5 ml. of concentrated ammonium hydroxide is held at 25°C for a period of 30 minutes. After removing the solvent by evaporation under reduced pressure, the residue is chromatographed on a 3.0×30 cm. column of diethylaminoethyl cellulose in the bicarbonate form. The column is washed with 250 ml. of water and then eluted with a linear gradient (0.002—0.2M) of aqueous triethylammonium bicarbonate at pH 7.5. The major ultraviolet absorbing peak is collected and evaporated to dryness under reduced pressure to yield the bistriethylammonium salt of [1-(2,5,6-trideoxy- β -D-erythro-hexofuranosyl)thymine] 6'-phosphonic acid.

EXAMPLE 14

A mixture of 1.76 g. of diethyl [9-(5,6-dideoxy-2,3-O-isopropylidene- β -D-ribo-hexofuranosyl)adenine] 6'-phosphonate and 1.8 g. of sodium iodide in 10 ml. of dimethylformamide is heated at 150°C for 20 hours. After cooling the reaction mixture, there is added 50 ml. of acetone. The resulting precipitate is collected and washed with several portions of acetone. The precipitate is then dissolved in water and passed through a column containing the free acid-form of an ion-exchange resin. The thus-obtained acidic eluate is concentrated under reduced pressure to one-half the original volume and then heated at 100°C for four hours to give an aqueous solution of [9-(5,6-dideoxy- β -D-ribo-hexofuranosyl)adenine] 6'-phosphonic acid. For purification, if desired, the pH of the eluate is adjusted to 8.5 with aqueous sodium hydroxide solution and the resulting mixture is chromatographed on a 4.0×40 cm. column of diethylaminoethyl cellulose in the bicarbonate form using a linear gradient (0.002 to 0.2M) of triethylammonium bicarbonate as eluant to afford the bistriethylammonium salt of [9-(5,6-dideoxy- β -D-ribo-hexofuranosyl)adenine] 6'-phosphonic acid.

An aqueous solution of the latter compound is passed through a column of cation-exchange resin in the acid-form, and the pH of the eluate is adjusted to 8.5 by the dropwise addition of aqueous sodium hydroxide solution. The eluate is then concentrated to a volume of approximately 10 ml., and added to 50 ml. of acetone to yield the disodium salt of [9-(5,6-dideoxy- β -D-ribo-hexofuranosyl)adenine] 6'-phosphonic acid as a white powder.

EXAMPLE 15

To a mixture of 512 mg. (1 mmole) of diphenyl [1-(5,6-dideoxy-2,3-O-isopropylidene- β -D-ribo-hex-5-enofuranosyl)uracil] 6'-phosphonate, 500 mg. of potassium azodicarboxylate in 20 ml. of methanol, is added dropwise 300 mg. of glacial acetic acid, and the reaction mixture is held at room temperature for a period of 24 hours. After this reaction time, the mixture is evaporated to dryness under reduced pressure and the residue partitioned between 50 ml. of ethyl acetate and 50 ml. of water. The aqueous layer is separated and extracted with several portions of ethyl acetate. The combined ethyl acetate layer and extracts are dried over magnesium sulfate, evaporated to dryness under reduced pressure to yield diphenyl [1-(5,6-dideoxy-2,3-O-isopropylidene- β -D-ribo-hexofuranosyl)uracil] 6'-phosphonate.

In a similar manner, by repeating the procedures of Examples 9, 10 and 11, the latter material is converted to the bis triethylammonium salt of [1-(5,6-dideoxy- β -D-ribo-hexofuranosyl)uracil] 6'-phosphonic acid.

EXAMPLE 16

A mixture of 92.7 g. of triphenylphosphine and 100.1 g. diphenyl chloromethylphosphonate is heated at 175° for three and one-half hours. The resultant solid mass is dissolved in about 1700 ml. water and about 500 ml. ether and the phases are separated. The ether layer is further extracted with about 250 ml. water. The combined aqueous phases are brought to pH 8 by the cautious addition of 10 N sodium hydroxide and the precipitate removed by filtration and dried to give diphenyl triphenylphosphoranylidene methylphosphonate which is crystallized from ethyl acetate.

EXAMPLE 17

A solution of 508 mg. of diphenyl triphenylphosphoranylidene-methylphosphonate in 10 ml. of methanol is heated under reflux for 30 minutes. Removal of the methanol by evaporation under reduced pressure gives a residual syrup which is crystallized from a mixture of ethyl acetate and hexane to give dimethyl triphenylphosphoranylidene-methylphosphonate.

EXAMPLE 18

To a stirred mixture of 4.82 g. (9 mmole) of diphenyl [9-(5,6-dideoxy-2,3-O-isopropylidene- β -D-ribo-hex-5-enofuranosyl)adenine] 6'-phosphonate and 9.0 g. of potassium azodicarboxylate (45 mmole) in 135 ml. of pyridine is added 54 g. of glacial acetic acid (90 mmole). The yellow suspension is stirred under anhydrous conditions in an argon atmosphere for 24 hours and then the pyridine is removed by evaporation under reduced pressure. The yellow residue is partitioned between water (250 ml.) and ethyl acetate (250 ml.) and the water phase is further extracted with ethyl acetate (2 \times 250 ml.). The organic phases are combined, washed with water (500 ml.), dried over magnesium sulfate, filtered and evaporated to dryness to give a pale yellow foam. This is dissolved in about 20 ml. of hot benzene and on cooling deposits white crystals which are collected to give diphenyl [9-(5,6-dideoxy-2,3-O-isopropylidene- β -D-ribo-hexofuranosyl)adenine] 6'-phosphonate.

EXAMPLE 19

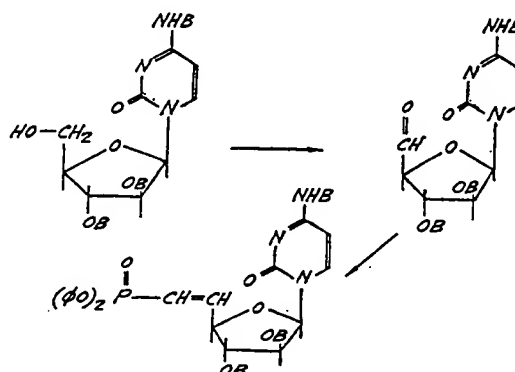
A solution of 5.14 g. (10 mmole) of diphenyl [-(5,6-dideoxy-2,3-O-isopropylidene- β -D-ribo-hexofuranosyl)uracil] 6'-phosphonate in 50 ml. of dimethyl sulfoxide is added rapidly at room temperature to a solution of 2.0 g. (42 mmoles) of sodium hydride (50% dispersion in mineral oil) in 20 ml. each of benzyl alcohol and dimethyl sulfoxide. After 15 minutes, the slightly yellow solution is poured into 250 ml. of water containing 3 ml. of glacial acetic acid. The resulting suspension is extracted with ethyl acetate (3 \times 200 ml.) and the combined extracts are washed with aqueous sodium bicarbonate and then water. The organic phase is then dried over magnesium sulfate, filtered and evaporated to dryness to give a pale yellow oil. A solution of this oil in chloroform (25 ml.) is then applied to the top of a silica gel column (35 \times 4.5 cm.). Development of the column with 1250 ml. chloroform and 650 ml. of ethyl acetate followed by elution with 1000 ml. 10% methanol in ethyl acetate gives dibenzyl [1-(5,6-dideoxy-2,3-O-isopropylidene- β -D-ribo-hexofuranosyl)uracil] 6'-phosphonate.

EXAMPLE 20

A solution of 4.52 g. of dibenzyl [1-(5,6-dideoxy-2,3-O-isopropylidene- β -D-ribo-hexofuranosyl)uracil] 6'-phosphonate in 100 ml. of methanol is added to a pre-reduced suspension of 2 g. of 5% palladium-on-barium sulfate in 100 ml. of methanol. The resultant mixture is stirred at room temperature under 1 atmosphere of hydrogen for 50 minutes at which time the theoretical volume of hydrogen has been consumed. The catalyst is removed by filtration through diatomaceous earth and the combined filtrate and washings are evaporated to dryness to yield a white foam which is redissolved in 50 ml. of water. The aqueous solution is passed down an acid ion-exchange column (2.5 \times 20 cm.) which is washed with water. The first 225 ml. of column eluant is heated at 100°C for one hour and then evaporated to dryness under reduced pressure. The residue is reevaporated several times from methanol solution and is then dissolved in 50 ml. of hot ethanol. The solution on cooling deposits a white micro-crystalline solid to yield [1-(5,6-dideoxy- β -D-ribo-hexofuranosyl)uracil] 6'-phosphonic acid.

EXAMPLE 21

The process of Example 7 is repeated using an equivalent amount of 1-(N⁴,O^{2',3'}-tribenzoyl- β -D-arabinofuranosyl)cytosine as the starting material and there is obtained diphenyl [1-(5,6-dideoxy-N⁴,O^{2',3'}-tribenzoyl- β -D-arabino-hex-5-enofuranosyl)cytosine] 6'-phosphonate. This conversion can be illustrated as follows wherein B represents benzoyl and Ø is phenyl:



Similarly, by using 1-(2',3'-di-O-benzoyl-β-D-arabinofuranosyl)thymine and 1-(2',3'-di-O-benzoyl-β-D-arabinofuranosyl)uracil in the process of Example 7, there is obtained diphenyl [1-(5,6-dideoxy-2',3'-di-O-benzoyl-β-D-arabino-hex-5-enofuranosyl)thymine] 6'-phosphonate and diphenyl [1-(5,6-dideoxy-2',3'-di-O-benzoyl-β-D-arabino-hex-5-enofuranosyl)uracil] 6'-phosphonate, respectively.

By repeating the process of Example 18, the above compounds are reduced to the corresponding arabinohexofuranosyl derivatives, that is, diphenyl [1-(5,6-dideoxy-N⁴,O^{2',3'}-tribenzoyl-β-D-arabino-hexofuranosyl)cytosine] 6'-phosphonate, diphenyl [1-(5,6-dideoxy-2',3'-di-O-benzoyl-β-D-arabino-hexofuranosyl)thymine] 6'-phosphonate and diphenyl [1-(5,6-dideoxy-2',3'-di-O-benzoyl-β-D-arabino-hexofuranosyl)uracil] 6'-phosphonate which are subjected to the processes of Examples 19 and 20 to give [1-(5,6-dideoxy-β-D-arabino-hexofuranosyl)cytosine] 6'-phosphonic acid, [1-(5,6-dideoxy-β-D-arabino-hexofuranosyl)thymine] 6'-phosphonic acid and [1-(5,6-dideoxy-β-D-arabino-hexofuranosyl)uracil] 6'-phosphonic acid.

EXAMPLE 22

The process of Example 19 is repeated using an equivalent amount of diphenyl [9-(5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hexofuranosyl)adenine] 6'-phosphonate and diphenyl [1-(3-O-acetyl-2,5,6-trideoxy-β-D-erythro-hexofuranosyl)thymine] 6'-phosphonate as the starting material and there is obtained dibenzyl [9-(5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hexofuranosyl)adenine] 6'-phosphonate and dibenzyl [1-(3-O-acetyl-2,5,6-trideoxy-β-D-erythro-hexofuranosyl)thymine] 6'-phosphonate, respectively, which are subjected to the process of Example 20 to yield [9-(5,6-dideoxy-β-D-ribo-hexofuranosyl)adenine] 6'-phosphonic acid and [1-(2,5,6-trideoxy-β-D-erythro-hexofuranosyl)thymine] 6'-phosphonic acid, respectively.

EXAMPLE 23

The process of Example 19 is repeated with the exception of using an equivalent amount of methanol in place of benzyl alcohol and there is obtained [1-(5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hexofuranosyl)uracil] 6'-phosphonate.

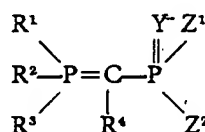
Similarly, by using ethanol there is obtained diethyl [1-(5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hexofuranosyl)uracil] 6'-phosphonate.

By subjecting the above compounds to the dealkylation procedure of Example 14, there is obtained the disodium salt of [1-(5,6-dideoxy-β-D-ribo-hexofuranosyl)uracil] 6'-phosphonic acid.

In view of the risk of infringement, attention is particularly directed to our co-pending application No. 3377/71 (Serial No. 1243214), divided from this specification, which claims the nucleoside 6'-phosphonic acids and nucleoside 6'-phosphonates herein disclosed.

WHAT WE CLAIM IS:—

1. A compound having the general formula:



wherein each of R¹, R² and R³ is lower alkyl (as herein defined) or aryl or substituted aryl (as herein defined);

or R¹, R² and R³ together are tri-N-piperidyl, tri-N-morpholinyl or tricyclohexyl; R⁴ is hydrogen, lower alkyl (as herein defined), cyclohexyl, or aryl or substituted aryl (as herein defined);

Y is oxygen or sulfur;

each of Z¹ and Z² is the group OR⁵, SR⁶,



or NR⁷R⁸ in which each of R⁵ and R⁶ is lower alkyl or lower alkenyl (as herein defined), or aryl or substituted aryl (as herein defined), and each of R⁷ and R⁸ is lower alkyl (as herein defined) or aryl (as herein defined); or

Z¹ and Z² together are the group $\begin{matrix} \text{O} & \text{O} & \text{S} \\ & \text{O} & \text{S} \end{matrix} > \text{R}^9$, $\begin{matrix} \text{O} & \text{O} & \text{S} \\ & \text{S} & \text{S} \end{matrix} > \text{R}^9$ or $\begin{matrix} \text{O} & \text{O} & \text{S} \\ & \text{O} & \text{S} \end{matrix} > \text{R}^9$ in which R⁹ is

alkylene or arylene.

2. A compound according to Claim 1 wherein Y is oxygen; and each of Z¹ and Z² is the group OR⁵ in which R⁵ is phenyl.

3. A compound according to Claim 1 wherein Y is oxygen; and each of Z¹ and Z² is the group OR⁵ in which R⁵ is substituted aryl.

4. A compound according to Claim 1 wherein Y is oxygen; and each of Z¹ and Z² is the group OR⁵ in which each of R⁵ is lower alkyl.

5. A compound according to Claim 1 wherein Y is oxygen; and each of Z¹ and Z² is the group



or NR⁷R⁸ in which each of R⁷ and R⁸ is alkyl or aryl.

6. A compound according to Claim 1 wherein Y is oxygen; and Z¹ and Z² together are the group $\begin{matrix} \text{O} \\ \text{O} \end{matrix} > \text{R}^9$ in which R⁹ is arylene.

7. A compound according to Claim 1 wherein Y is oxygen; and each of Z¹ and Z² is the group OR⁵ in which R⁵ is benzyl.

8. A compound according to Claim 1 wherein Y is sulfur; and each of Z¹ and Z² is the group OR⁵ in which R⁵ is lower alkyl (as herein defined).

9. A compound according to Claim 1 wherein Y is sulfur; and each of Z¹ and Z² is the group OR⁵ in which R⁵ is phenyl.

10. A compound according to Claim 2 wherein each of R¹, R², and R³ is phenyl; and R⁴ is hydrogen or methyl.

11. A compound according to Claim 3 wherein each of R¹, R² and R³ is phenyl; R⁴ is hydrogen; and R⁵ is *p*-nitrophenyl.

12. A compound according to Claim 3 wherein each of R¹, R² and R³ is phenyl; R⁴ is hydrogen; and R⁵ is *p*-nitrobenzyl or *p*-bromobenzyl.

13. A compound according to Claim 4 wherein each of R¹, R² and R³ is phenyl; R⁴ is hydrogen; and R⁵ is ethyl.

14. A compound according to Claim 5 wherein each of Z¹ and Z² is morpholinyl.

15. A compound according to Claim 6 wherein each of R¹, R² and R³ is phenyl; R⁴ is hydrogen; and R⁵ is *o*-phenylene.

16. A compound according to Claim 7 wherein each of R¹, R² and R³ is phenyl; and R⁴ is hydrogen.

17. A compound according to Claim 8 wherein each of R¹, R² and R³ is phenyl; R⁴ is hydrogen; and R⁵ is ethyl.

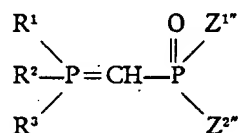
18. A compound according to Claim 9 wherein each of R¹, R² and R³ is phenyl; and R⁴ is hydrogen.

19. A compound according to Claim 14 wherein each of R¹, R² and R³ is phenyl; and R⁴ is hydrogen.

20. A process for the conversion of a nucleoside 5'-aldehyde into a nucleoside 6'-phosphonic acid in which saturation at the 5',6'-carbon-carbon saturated bond is performed by catalytic hydrogenation or by diimide reduction of a corresponding carbon-carbon ethylenically unsaturated bond; and in which each of the hydroxy

groups on the phosphorus atom is formed by hydrolysis, hydrogenolysis, anionic dealkylation, enzymatic action or combinations thereof of the appropriate $Z^{1''}$ or $Z^{2''}$ groups; which includes:

- 5 reacting in a substantially anhydrous non-reactive organic solvent
 1) a nucleoside 5'-aldehyde with
 2) a phosphorylated phosphonium ylid of the general formula



- 10 wherein each of R^1 , R^2 and R^3 is lower alkyl (as herein defined) or aryl or substituted aryl (as herein defined); or R^1 , R^2 and R^3 together are tri-N-piperidyl, tri-N-morpholinyl or tricyclohexyl; R^4 is hydrogen, lower alkyl (as herein defined), cyclohexyl or aryl or substituted aryl (as herein defined); each of $Z^{1''}$ and $Z^{2''}$ is the group OR^5 , SR^6 ,



- 15 or NR^7R^8 in which each of R^5 and R^6 is lower alkyl or lower alkenyl (as herein defined), aryl or substituted aryl, and each of R^7 and R^8 is lower alkyl; or $Z^{1''}$ and $Z^{2''}$ together are the group $\begin{array}{c} O \\ | \\ >R^9 \end{array}$, in which R^9 is arylene.

- 20 21. The process according to Claim 20, wherein each of $Z^{1''}$ and $Z^{2''}$ is the group OR^5 in which R^5 is phenyl; and said first OR^5 group is removed by hydrolysis with base and said second OR^5 group is removed by enzymatic action with a snake venom phosphodiesterase.

22. The process according to Claim 21, wherein each of R^1 , R^2 and R^3 is phenyl.

- 25 23. The process according to Claim 20, wherein each of $Z^{1''}$ and $Z^{2''}$ is the group OR^5 in which R^5 is phenyl or naphthyl; and said OR^5 groups are converted to aralkyloxy groups by treatment with an aralkyl primary alcohol in the presence of base in an anhydrous dipolar organic solvent and said aralkyloxy groups are converted to hydroxy groups by catalytic hydrogenolysis.

24. The process according to Claim 23, wherein R^6 is phenyl in each of $Z^{1''}$ and $Z^{2''}$; said alcohol is benzyl alcohol, said base is an alkali metal hydride and said catalytic hydrogenolysis is carried out with a palladium catalyst.

- 30 25. A compound according to Claim 1 substantially as herein described and exemplified.

26. A process according to Claim 20 or Claim 23 substantially as herein described and exemplified.

- 35 27. A nucleoside 6'-phosphonic acid obtained by the process claimed in any one of Claims 20 to 24 or Claim 26.

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